Self-reported adverse drug reactions and adherence of dolutegravir containing antiretroviral therapy regimens among patients in Ayder Comprehensive Specialized Hospital, Mekelle City, Tigray region, Ethiopia

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This is to certify that the thesis prepared by **Goitom Belay Kassa**, entitled with "***Self-reported adverse drug reactions and adherence of dolutegravir containing antiretroviral therapy regimens among patients in Ayder Comprehensive Specialized Hospital, Mekelle City, Tigray region, Ethiopia***" and submitted in partial fulfillment of the requirements for Degree of Master of Sciences in Pharmacy Practice complies with the regulation of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Background: Despite being introduced into the ART regimen recently due to its many advantages, the tolerability of dolutegravir (DTG) has been questioned because of adverse reactions resulting in medication non-adherence and discontinuations. Therefore, this study aimed to assess self-reported adverse reactions and medication adherence of dolutegravir (DTG) based first line combination antiretroviral therapy (cART) at Ayder Comprehensive Specialized Hospital.

Method: A hospital based cross-sectional study was conducted from July to September 2022. Data were collected from medical records of patients and face to face interview. Statistical Package for Social Science (SPSS) window version 25 was used to analyze the data. The continuous and categorical variables were reported by mean/SD and frequency/percentage, respectively. Multivariate logistic regression was performed to identify predictors. Statistical significance was set at p-value <0.05.

Result: From a total of 357 participants**,** 38.9% (139) developed at least one adverse drug reaction. The most frequent reported ADRs were weight gain (21.8%), headache (19.6%) and insomnia (10.6%). Rural residence (AOR=0.362, 95%CI (0.134-0.977), p=0.045), WHO stage 1&2 (AOR=8.582, 95% CI (1.669-44.136), p=0.010), and co-medications (AOR=2.606, 95%CI (1.116-6.086), p=0.027), were significantly associated with self-reported adverse drug reactions in the multivariate analysis. In this study suboptimal adherence (84.6%) was reported. Participants who did not use co-trimoxazole prophylaxis (AOR=0.402, 95%CI (0.181-0.893), p=0.025), were found to be significantly associated with self-reported non-adherence.

Conclusion: A substantial number of ADRs associated with DTG based cART were reported in the study setting. Residence, WHO stage at entry and co-medications were significant predictors of ADRs. The level of medication adherence among the participants was suboptimal and participants who did not take cotrimoxazole prophylaxis were associated with poor adherence.

Key words: Self-reported, Adverse Drug Reactions, Dolutegravir, Adherence, Ayder Comprehensive Specialized Hospital

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Table of Contents

List of abbreviations and acronyms

3TC	Lamivudine
ACSH	Ayder Comprehensive Specialized Hospital
ADRs	Adverse Drug Reactions
AEs	Adverse Events
AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted odds ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
cART	Combined antiretroviral therapy
CD4 cells	Cluster of differentiation cells
CI	Confidence Interval
COR	Crude odds ratio
CPT	Cotrimoxazole Prophylaxis Therapy
DTG	Dolutegravir
EFV	Efavirenz
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immune Deficiency Virus
HR	Hazard Ratio
IPT	Isoniazid Preventive Therapy
MMAS-8	Morisky Medication Adherence Scale 8
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPSAEs	Neuropsychiatric Adverse Effects
NRTIs	Nucleoside reverse transcriptase inhibitor
OR	Odds ratio
PLWHA	People living with HIV/AIDS
PLWHIV	People living with HIV/AIDs
SPSS	Statistical Package for Social Science
TB	Tuberculosis

TDF	Tenofovir Disoproxil Fumarate
UNAIDS	Joint United Nations Programme on HIV and AIDS
WHO	World Health Organization

List of tables

List of figure

1. Introduction

1.2 Background

Human Immunodeficiency Virus (HIV) is a viral infection that attacks and destroys the body‘s immune system, particularly the white blood cells named CD4 cells(WHO, 2022). HIV remains one of the most prominent public health problems in the world. Although HIV/AIDS treatment and access have been successfully implemented, its global incidence was at nearly 40 million, the majority of whom are of productive age. Globally, in 2022, at least 1.3 million people were newly infected with HIV, 86% of the people living with HIV knew their status, 89% were accessing treatment and 93% were virally suppressed(UNAIDS, 2023).

Eastern and Southern Africa remain among the most exceedingly hit regions by the pandemic, accounting for almost two-thirds of the global total HIV cases. In Ethiopia, the second-highest-populated nation in Africa, 610,350 individuals were living with HIV of whom 83% were on ART at the end of 2022 with an estimated prevalence of 0.91% nationally. Tigray region is one of the districts with the highest prevalence (1.24%)(Ministry of Health, 2023).

Since there’s no known cure for HIV as of now, antiretroviral therapy (ART), which involves three or more drugs in combination, is the foremost effective intervention of HIV disease control (Li et al., 2021, Anstett et al., 2017). HIV-related morbidity and mortality have essentially decreased in both developed and developing countries since the introduction of cART. By boosting survival and lowering opportunistic infections through viral load reduction and CD4 T cell elevation, it also improves the quantity and quality of patients’ productivity (Weldegebreal et al., 2016, Ayele et al., 2017). The goal for 2025 is set to achieve viral suppression in 95% of individuals on ART. An important plan to achieve this goal, apart from promoting ideal adherence, is using a safer ART regimen(Abah et al., 2018, UNAIDS, 2023).

Among the diverse ART regimens, integrase strand transfer inhibitors (INSTIs) are the latest class developed to target HIV enzymes, recommended for both ART-experienced and ART-naïve patients. Dolutegravir (DTG), a second-generation INSTI, has shown high efficacy and a strong resistance barrier (Hurbans and Naidoo, 2024).

It also has the benefits of fewer drug interactions, less unfavorable reactions, better adherence resulting from its single daily dose, and a quick viral suppressive effect(Yadav et al., 2018).

The World Health Organization (WHO) has advised countries with pretreatment resistance to Efavirenz(EFV) or Nevirapine (NVP) of 10% or more to switch to alternative antiretroviral drugs (WHO, 2018, Kumarasamy et al., 2019, Mondi et al., 2019). In Ethiopia, DTG has been recommended as the preferred first-line ARV. This regimen is applied to all newly diagnosed adults, those with undetectable viral loads, and patients experiencing side effects from NNRTIS (Federal Ministry of Health Ethiopia, 2018).

While the use of combination antiretroviral therapy (cART), such as DTG-based ART, improves the quality of life and survival rates for people living with HIV/AIDS (PLWHA), it is associated with adverse drug reactions (ADRs) of varying severities over the short and long term. ADRs, which are harmful and unintended responses to medications taken at standard doses for prevention, diagnosis, or treatment, are major factors leading to treatment discontinuation, regimen switching, and suboptimal adherence. These issues can result in poor clinical outcomes (Mendes et al., 2018, Ejigu et al., 2018, Anbessa et al., 2024).

Individuals living with HIV (PLWH) have to be exceedingly adhered to their treatment for the drug to be effective for a long period and to prevent the emergence of resistant viral strains (Cevik et al., 2020, Benson et al., 2020). Nevertheless, adherence is a complex health behavior that's impacted by the drug regimen, patient and family-related variables, and the patient-health provider connection(Tekle et al., 2024).

The safety profile of ARV drugs among patients on dolutegravir-based first-line ART regimen in Ethiopia, particularly in the study area, is minimal. The study therefore, conducted to get scientific information on the profile of ADRs related with dolutegravir- based ART and its impact on self-reported adherence, as well as factors related with it, with the ultimate goal of improving its tolerability and adherence by PLWH to HIV treatment.

1.2 Statement of the problem

Antiretroviral therapy (ART) has significantly extended the lifespan and improved the quality of life for individuals living with HIV/AIDS (PLWHA). However, long-term ART introduces new challenges, including drug-related toxicity and intolerance, which can negatively impact quality of life, lead to treatment interruptions, and reduce adherence. These issues can also promote the emergence of resistant virus strains, complicating treatment and increasing its cost(Mwanthi, 2020, Yunita et al., 2023).

The tolerability of DTG has been questioned by recent observational studies and post-marketing pharmacovigilance, leading to high discontinuation rates due to side effects. Adverse drug reactions (ADRs), including treatment discontinuation and non-adherence, greatly elevate the risk of virologic failure, necessitating the use of more costly and challenging second-line ART regimens, especially in resource-limited countries (Abah et al., 2018).

Given the number of people who are and will be using the new cART, there is a need to monitor the safety profile of the drugs and maintain the safety of those using them. This monitoring is carried out in Ethiopia by the National pharmacovigilance center under the Food, Drug and Healthcare Administration (EFDA). This center report indicates that more than three-quarters of adverse reactions are due to antiretroviral drugs (FMHACA, 2016). However, for various reasons, this organization is only able to collect and record a small number of reports from health facilities (Hailu and Mohammed, 2020).

Because it has never been easier to achieve a near-ideal rate of >95%, the threshold needed to achieve viral suppression, prevent the recurrence of opportunistic infections; non-compliance is a widespread concern globally. Adherence is a complex process that requires a multifaceted strategy; failure to do so could have disastrous consequences for the program, the healthcare system, and society as a whole (Soares and Araújo, 2020).

The development of drug-resistant HIV strains and their immediate adverse health effects contribute to increased risk of opportunistic infections as well as increased morbidity and mortality from HIV infection when not follow the recommended treatment regimen.

Therefore, it is essential to understand the frequency, pattern of adverse reactions, and medication adherence in people living with HIV receiving DTG-based antiretroviral therapy to inform clinical decision-making and ultimately improve outcomes.

Limited published data on switching to DTG-based regimens demonstrates significant rates of adverse drug reactions and discontinuations. To date, studies on adverse drug reactions and treatment adherence in patients receiving dolutegravir-based regimen are limited in Ethiopia. Therefore, this study aimed to evaluate the occurrence of adverse reactions and medication adherence in patients receiving dolutegravir based ART regimens at Ayder Comprehensive Specialized Hospital (ACSH).

1.3 Significance of the Study

The results of this study have implications for the identification and management of adverse drug reactions (ADRs) by healthcare professionals as well as for individuals living with HIV/AIDS. Adverse reactions are linked with poor adherence to antiretroviral (ARV) drugs, which can lead to treatment failure and the emergence of multidrug-resistant viruses. Damage caused by ADRs can be permanent or irreversible even after stopping taking the offending drug. Rapid detection, prevention, and management of adverse reactions can significantly improve and prolong the quality of life of HIV-infected patients.

In Ethiopia, the DTG combination was introduced as the first-line treatment regimen. Therefore, it is important to evaluate the safety of this new treatment regimen. Additionally, it will enable various stake holders, including regulators, policymakers, healthcare professionals, governmental and non-governmental organizations and concerned individuals to care of HIV patients, creating plans to improve the delivery of safe HIV care services.

ADR studies also allowed a more comprehensive understanding of the safety profile of cART. Furthermore, knowing the risk factors associated with adverse reactions in a specific population may help identify patients at risk of adverse reactions, which may lead to the implementation of appropriate measures, such as monitoring the patient more closely early. As a result, first-line regimens will be more sustainable, and these patients will remain linked to the services and ensure adherence to cART.

The success of treatment program depends heavily on adherence, and adherence support is essential in the treatment of HIV-infected patients. Medication adherence is difficult for most chronic diseases, but is especially difficult for people with HIV/AIDS. Additionally, suboptimal adherence may accelerate the development of drug-resistant HIV and undermine the role of cART in reducing HIV incidence and transmission. Promoting treatment adherence is, therefore, important as these treatments become increasingly for people living with HIV (PLHIV) in developing countries, where monitoring is often challenging.

2. Literature review

Antiretroviral therapy (ART) has significantly reduced both morbidity and mortality rates among individuals with HIV by effectively suppressing viral replication and enhancing the immune system's response. This treatment approach has led to substantial improvements in the health and longevity of HIV-positive patients, transforming what was once a fatal diagnosis into a manageable chronic condition.

Currently a WHO and Ethiopian guidelines recommends dolutegravir (DTG) plus a NRTI backbone to be preferred when initiating PLHIV on ART. Dolutegravir, which is a second generation INSTI, is known to be better tolerated, has high potency and has a high genetic barrier to HIV drug resistance.

While antiretroviral therapy (ART), particularly regimens based on dolutegravir (DTG), has greatly enhanced the prognosis and lifespan of individuals with HIV, it is not without its drawbacks. Adverse drug reactions (ADRs) are common with ART and can manifest immediately, early, or late. These reactions can range from mild to severe and even life-threatening. ADRs may lead to the discontinuation of treatment, suboptimal adherence, reduced treatment efficacy, and increased morbidity and mortality rates.

This literature review offers a thorough overview of adverse reactions and adherence in HIV-positive patients receiving DTG-based ART.

Magnitude and predictors of adverse drug reactions of ART

The occurrence of adverse reactions among people living with HIV/AIDS on dolutegravir (DTG)-based ART varies significantly across different populations and sites. Multiple studies have found ADRs to be the most common reason for patients on combination ART to modify or discontinue their treatment regimen. Research in both developing and developed countries has indicated elevated rates of ADRs in patients, regardless of whether they are treatment-naïve or treatment-experienced, when receiving a DTG-based ART regimen.

A research conducted by Hurbans and Naidoo (Hurbans and Naidoo, 2024) in South Africa identified a higher prevalence of ADRs (43.6%,461) associated with DTG based ART regimen.

Similarly, Nabitika et al (Nabitaka et al., 2020) in Uganda found that 43% and 33% of 365 patients reported experiencing at least one side effect at one month and six months, respectively. Likewise, sixty adverse events (AEs) out of forty-five spontaneous ADR reports were found in a study by (Chilambe et al., 2019)that sought to describe AEs experienced and reported among patients on DTG-based regimens for HIV therapy in Zambia. A study conducted by(Mendes et al., 2018) in Brazil reported a prevalence of (81%,106) . The differences observed in the rate of adverse reaction among HIV-positive patients receiving dolutegravir (DTG)-based antiretroviral therapy (ART) can be attributed to variations in study design, patient population characteristics, and the approaches used for ADR evaluation.

A systematic review of thirty three studies with a total sample of 138 466 people received a DTG-based ART in 13 countries, reviled the frequently reported types of ADRs encompassed Central nervous System (33%), Gastrointestinal symptoms (33%), Neuropsychiatric (30%), Skin ADRs (18%) and weight gain (12%) (Wadesango, 2022). A study in Uganda ((Nabitaka et al., 2020)), found Central Nervous system adverse effects to be the most often reported followed by fatigue and difficulty in sleeping. Higher rate of discontinuations was reported by Nasreddine *et., al* conducted in six leading HIV reference centers in Belgium on four thousand, one hundred and one patients both treatment naïve and experienced. DTG was stopped in 785 cases (19.1%). ADRs accounted for 9.5% of all discontinuations, with neuropsychiatric symptoms accounting for the highest percentage (5.2%) (Nasreddine et al., 2020). The three most common AEs linked to DTG use were found to be nausea (13.34%), diarrhea (9.83%), and headaches (9.23%) in another study conducted in Brazil between April and December 2017 in an effort to describe the planning and implementation process of the active pharmacovigilance of DTG project (Batista et al., 2019).

Numerous predictors have been associated with an increased likelihood of experiencing adverse reactions in HIV patients receiving antiretroviral therapy (ART). These include advanced age, female gender, CD4 count, concomitant use of other medications, the specific ART regimen prescribed, and the presence of comorbidities. A retrospective cohort study in Germany conducted on 1704 participants revealed higher prevalence of neuropsychiatric adverse drug reactions among women and patients who were older than 60 years (Hoffmann et al., 2017).

Likewise, a study in Zambia found that neurological and neuropsychiatric symptoms(30%) followed by impaired feelings of balance (16.7%) were to be more likely to occur on patients over 50 years old(Chilambe et al., 2019). The heightened risk of adverse reactions in female HIV patients can be explained by sex-related physiological differences, such as lower body weight, variations in enzyme activity, and reduced renal clearance. Furthermore, women's greater use of additional medications like contraceptives and supplements may also contribute to their increased susceptibility to ADRs (Zucker and Prendergast, 2020).

A Netherlands cohort analysis of both treatments experienced and naïve patients receiving DTG-based regimens revealed a significant proportion of discontinuations owing to adverse events. A total of 556 patients had 85 (15.3%) discontinuations noted, with 13.7% (76 patients) attributed to adverse events attributable to the treatment. The most common ADRs attributing for switching DTG were sleep disturbances (5.6%), gastrointestinal complaints (4.3%), and neuropsychiatric symptoms (4.3%). DTG was switched more frequently in regimens including Abacavir (adjusted relative risk 1.92, 95% confidence interval 1.09–3.38, P=0.01)(de Boer et al., 2016). Similar to this study, patients who were HLA-B*5701- negative and started Abacavir were reported to be more likely to experience ADRs associated with DTG based ART use (Hoffmann et al., 2017).

The stage of HIV disease at the initiation of antiretroviral therapy (ART) has also been identified as an independent risk factor for adverse drug reactions (ADRs) in adult HIV patients. Specifically, studies have shown that patients who start ART at more advanced clinical stages, such as WHO stage III or IV, have a significantly higher risk of experiencing ADRs compared to those who begin treatment at earlier clinical stages (WHO stage I or II)(Abah et al., 2015).The increased ADR risk in HIV patients with advanced clinical disease is likely due to their higher susceptibility to opportunistic infections, necessitating the use of multiple medications, which can disrupt pharmacodynamics and pharmacokinetic mechanisms and heighten the potential for adverse drug interactions(Dahiya, 2018).

The variability observed in the prevalence of adverse drug reactions (ADRs) among HIV-positive patients receiving antiretroviral therapy (ART) can be attributed to a confluence of factors. These include individual patient characteristics; the specific ART regimen prescribed; as well as the methodologies employed for ADR monitoring and assessment.

Adherence and associated predictors of PLWHA to ART

ART must be taken regularly for life to maintain viral suppression in those infected with HIV. To sustain virologic suppression and stop emergence of drug resistance, current clinical practice has prioritized maintaining an ART adherence threshold of 95% or higher (Catalano, 2022, Do, 2011). Prolonged use of ARVs, however, presents risks of intolerance and drug-related toxicities, both of which have a direct negative impact on adherence. The results of many studies carried out in Ethiopia showed that the range of optimal adherence is 72.4% to 94.3%, indicating that HAART adherence is still below optimal levels (Tegegne et al., 2022).

Drug choices for PLHI are limited due to drug resistance, elevated viral load, and increased morbidity and mortality resulting from suboptimal adherence to DTG-based regimens. Inadequate adherence raises the cost and complexities of the condition, puts a pressure on the health budget, which hinders economic growth, and decreases the gross domestic product (Namakula et al., 2023, Cardoso et al., 2019).

Worldwide, adherence is a problem that is influenced by a number of personal, pharmaceutical, and healthcare-related variables. Major HAART problems arise early in the course of treatment and factors such as poor outcomes, the quantity of pills taken, the degree of education, the existence of AIDS symptoms, and other things that directly affect the patient's routine are the key affecting adherence. Across all age categories, forgetting, being away from home, despair, and a break in daily routine were the most commonly stated individual barriers; adults and adolescents were more likely to indicate alcohol and/or substance dependence. Obstacles pertaining to health services, such as stock outs and clinic distance, were also commonly noted (Cardoso et al., 2019, Shubber et al., 2016, Inoue et al., 2023).

Negative consequences of ADRS can lead to non-compliance, stigmatization, low self-esteem, and psychological distress, potentially contributing to patients' inability to adhere to their treatment regimen (Oliveira et al., 2018, Mwanthi, 2020).Determining the patient's preparedness for cART, including awareness of and managing of possible side effects, is essential before the initial prescription. This is because adhering to treatment for HIV infection is challenging and ADRs have a detrimental effect on medication adherence.

Conceptual framework

Self-reported adverse medication responses and adherence among adult HIV patients on DTG-based ART regimen were the study's primary goals. Data from clinical trials and observational studies reported neuropsychiatric, gastrointestinal, weight gain and hypersensitivity skin reactions as the most reported adverse drug reaction among patients on DTG-based ART regimen. Different literatures also suggest that both socio-demographic and clinical factors predispose one to adverse drug reactions. The adherence of HIV patients to their antiretroviral (ARV) regimen can be significantly impacted by the various factors that contribute to the occurrence and severity of adverse drug reactions (ADRs) (Figure 1).

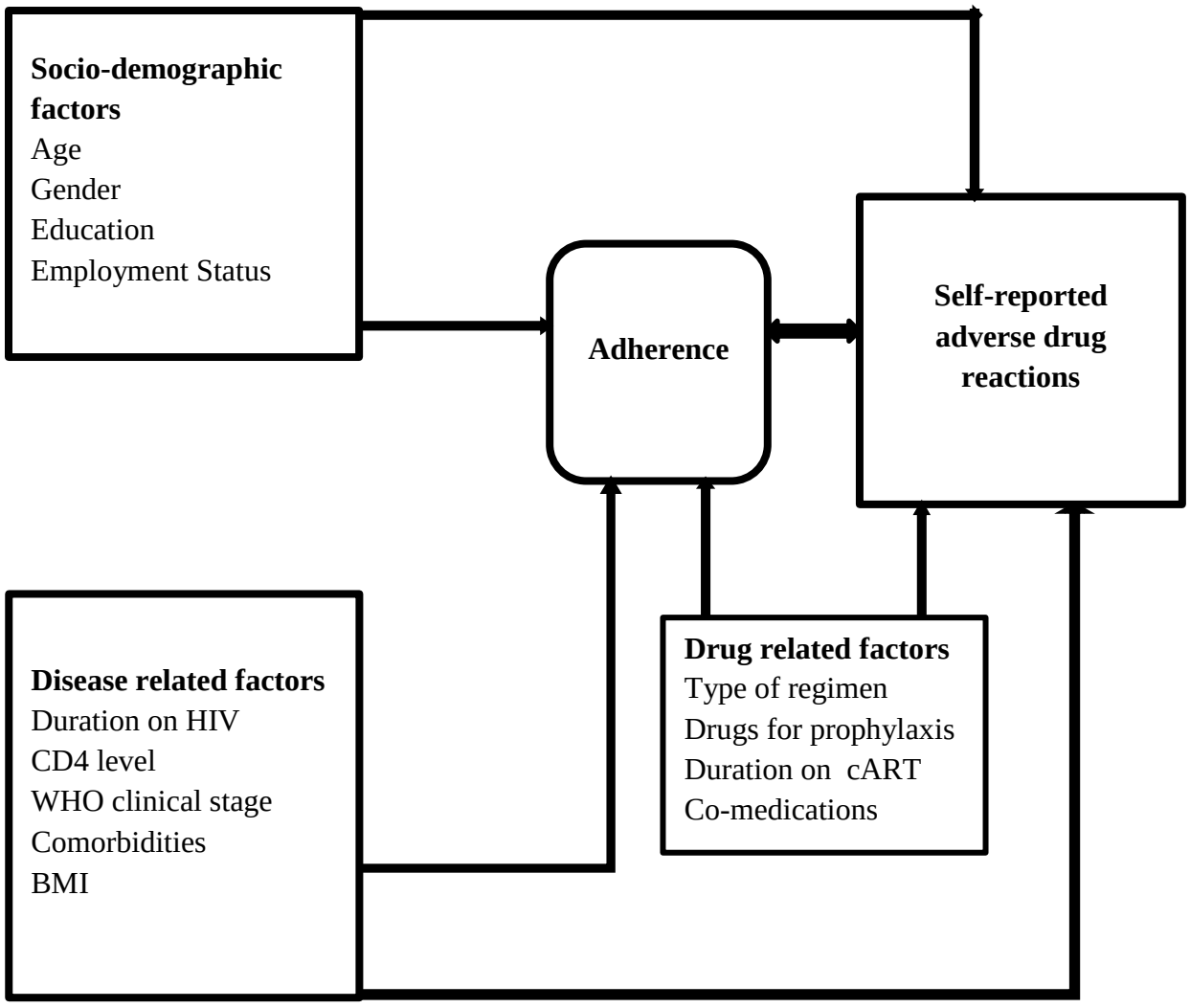

Figure 1: Conceptual framework that shows the factors associated with ADRS of DTG based ART regimen at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022

3. Objectives

3.1 General objective

To determine the prevalence of self-reported adverse reactions and adherence of dolutegravir (DTG) containing antiretroviral therapy regimens of study participants at Ayder Comprehensive Specialized Hospital.

3.2 Specific objectives

- To assess the prevalence of adverse reactions of study participants on DTG based first line cART regimen
- To describe the common types of adverse reactions of study participants on DTG based first line cART regimen
- To determine the factors associated with the occurrence of ADR of study participants on dolutegravir based first line cART regimen
- To assess the level and factors associated with non-adherence of study participants on dolutegravir based first line cART regimen

4. Methodology

4.1 Study Area

The study was conducted in ART clinic of Ayder Comprehensive Specialized Hospital (ACSH) which is located in Northern part of Ethiopia, Tigray region, Mekelle city, 783 km far from Addis Ababa, the Capital city of Ethiopia. About 9 million people live in its catchment areas, which are in Tigray, Afar, and the southeast of the Amhara Regional States. It provides a wide range of medical treatments to patients of all ages, both in and out of the hospital. The ACSH has a total capacity of approximately 500 inpatient beds and additional specialist units. It also serves as a teaching hospital for Mekelle University's College of Health Sciences. The HIV clinic in ACSH provides antiretroviral therapy (ART) for approximately 2400 people living with HIV (PLHIV).

4.2 Study design and period

A hospital based cross-sectional study was conducted among patients who were on dolutegravir based first line cART and the data were collected from July, 2022 to September 2022.

4.3 Population

4.3.1 Source population

HIV infected adult patients on dolutegravir based first line cART regimen on follow-up in ART clinic at ACSH.

4.3.2 Study population

HIV infected adult patients on dolutegravir based cART regimen on follow-up in ART clinic at ACSH and fulfilling the eligibility criteria were enrolled.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

- Patients who were on dolutegravir based first line regimen
- HIV/AIDS patients who were 18 years old and above
- Patients who had three months or more of follow up at the ART clinic.

4.4.2 Exclusion criteria

- Patients who did not give consent to participate in the study.
- Patients with cognitive impairment and critically ill.

4.5 Sampling

4.5.1 Sample size determination

The sample size was calculated based on a single population proportion formula by taking 50% prevalence to achieve a maximum sample size. The total number of HIV/AIDS patients taking DTG based ART were 1900 patients.

$$N = \frac{Z^2\alpha\, P(1-P)}{\delta^2}$$

Where, P=50% using 95% confidence level, Zα=1.96, and δ=0.05; the calculated sample size was 384. Considering 5% of contingency, the final sample size was, hence, 403 patients.

4.5.2 Sampling procedures

Using systematic random sampling method, patients were selected from the waiting room of ART clinic, on the day of their visit to refill ART medications.

$$K= N/n = 1900/403 \approx 4.7= 5$$

Where K= Sampling interval; N= Source population; n= Sample size

The first person was selected random. Then every 5th patient was included in the sample. Those patients who did not fulfill the inclusion criteria were substituted with the next patient on the list.

4.6 Study variables

4.6.1 Independent variables

Socio-demographic characteristics: Gender, Age, Marital status, Educational status, Employment status, Religion, Residence

Clinical and laboratory characteristics: Baseline WHO stage, Current CD4, Weight/Height (BMI), Comorbidities,

cART-related characteristics: Treatment Naïve/ experienced, Initial regimen, duration on initial regimen, current regimen, duration on current regimen.

4.6.2 Dependent variables

- Self-reported adverse drug reactions
- Adherence level

4.7 Data collection and management

4.7.1 Data collection form

The questionnaire was prepared in English, then translated into Tigrigna and back translated into English to check for consistencies. The questionnaire contains socio-demographic, clinical and

laboratory information, ART information, MMAS-8 adherence questions and lists of ADRS associated with DTG based cART.

4.7.2 Data collectors' recruitment and training

Three BSc nurses interviewed patients and reviewed medical records to gather data. Before beginning the actual data gathering process, the primary investigator trained them on the study's purpose, data collection tool, and extraction technique. Data gathering was overseen and handled by one BSc nurse. It was the primary investigator's responsibility to ensure that the data collection was completed.

4.7.3 Data Quality Control

The principal investigator gave training to the data collectors to guarantee the quality of the data. To ensure that the data collection tool was adequate, the data extraction format was pre-tested on 5% of the sample size. Any confusion or vagueness discovered throughout the pre-testing process was cleared up, and changes were made as necessary. To guarantee the accuracy and consistency of the data gathered, the primary investigator regularly reviewed the data collection procedure.

4.7.4 Data analysis procedures

After being cleaned, the data were coded and loaded into SPSS version 25, a statistical package for social sciences. Frequency tables and figures were used to display the categorical variables. To investigate associations, the continuous variables were stratified into subgroups. In the univariate analysis, variables with p values equal to or less than 0.20 were chosen to be included in the final model. The logistic regression results were displayed as odds ratios (OR) with their respective 95% confidence intervals. Statistical significance was set at p-value <0.05.

4.8 Ethical considerations

The Ethics Review Committee of Addis Ababa University's College of Health Sciences, School of Pharmacy, granted ethical approval (ref. no. ERB/SOP/209/11/2020). In addition, permission was sought from the medical director and department of internal medicine, School of Medicine of ACSH (ref. no. CHS-092pharmacy-13).

Informed consent was obtained from the study participants before data collection. By omitting identifiers, such as name or any other personal identifier, all information provided was kept private. Regarding the findings, no patient or healthcare provider name was disclosed.

4.9 Operational definitions or definition of terms

Adverse Drug Reaction: This term describes any unfavorable symptoms that patients have experienced and believed to be related to using ART that contains dolutegravir. We asked respondents if they have dealt with any of the many alternatives on the list. Patients were also requested to report any additional adverse drug reactions (ADRs) experienced while receiving DTG-based therapy.

Co-morbidity: is the term used to describe any disorders such as diabetes, hypertension, and heart failure and others out of HIV/AIDS that a patient may have experienced.

Adherence: is the degree to which a person complies with agreed-upon suggestions from a health care provider in terms of taking drugs, adhering to a diet, or other lifestyle changes. It is measured by the Morisky's 8-item Therapeutic Adherence Scale. The MMAS-8 scoring ranged from 0-8. In this study, we classified the PLHIV respondents into two groups: respondents with scores ≥ 6 points were classified as Good adherents, and respondents with scores < 6 points were classified as Poor adherents for the purpose of clarifying causes of poor adherence(Morisky, 2008).

4.10 Dissemination of findings

This study will be presented in the School of Pharmacy, College of Health Sciences, Addis Ababa University, and shared to Ayder Comprehensive Specialized Hospital, and the findings will be published in a reputable national or international journal to disseminate for scientific community.

5. Results

5.1 Socio-demographic characteristics of the participants

From 403 participants who were approached, a response rate of 89% was achieved. More than half of the study participants were female (51.5%). Majority (59.1%) of the respondents were in the age group of 40-59 years, with a mean age of 44 years. Nearly half (48.2%) of the participants were married. One hundred forty seven participants (41.2%) had primary level education, and 321(89.9%) were from urban dwellings (Table 1).

Table 1: Socio-demographic characteristics of study participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022(n=357).

Characteristics	Category	Frequency (n=357)	Percentage (%)
Sex	Male	173	48.5
	Females	184	51.5
Age	18-39	106	29.7
	40-59	211	59.1
	≥ 60	40	11.2
Marital status	Single	54	15.1
	Married	172	48.2
	Divorced	80	22.4
	Widowed	51	14.3
Education	Illiterate	76	21.3
	Primary	147	41.2
	Secondary	59	16.5
	Diploma and above	73	20.4
Religion	Orthodox	320	89.6
	Non-orthodox	37	10.4
Residence	Urban	321	89.9
	Rural	35	9.8
Employment Status	Employed	102	28.6
	Unemployed	254	71.1

5.2 Clinical characteristics of the participants

With regard to clinical status, a mean level of CD4 cells/mm^3 was 470±238.7 and mean BMI was 22±3.9 kg/m^2. Three-fifth of participants' (59.1%) CD4 count level was at least 350 cells/mm^3 and were classified as WHO stages 1 and 2 (94.1%). Majority of the participants were treatment experienced (87.1%) and had received ART for more than 10 years (40.1%). Near two-third participants were on TDF/3TC/EFV based ART before switching (59.4%) (Table 2).

Table 2: Clinical and immunological characteristics of study participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022(n=357).

Characteristics	Category	Frequency (n=357)	Percentage (%)
BMI (kg/M2)	<18.5	61	17.1
	18.5-24.9	212	59.4
	>25	80	22.4
Duration since HIV diagnosis (years)	<5	67	18.8
	5-10	122	34.2
	>10	167	46.8
WHO stage	1 and 2	336	94.1
	3 and 4	21	5.9
Current CD4 count	<200cells/mm3	35	9.8
	200-350cells/mm3	68	19.0
	≥ 350cells/mm3	211	59.1
Treatment status	Naïve	44	12.3
	Experienced	311	87.1
Duration since start of treatment	<5years	31	8.7
	5-10years	117	32.8
	>10years	143	40.1
Regimen taken before switching	ZDV/3TC/NVP	60	16.8
	ZDV/3TC/EVF	16	4.5
	TDF/3TC/NVP	21	5.9
	TDF/3TC/EFV	212	59.4
Duration on DTG based ART	<2year	93	26.1
	>=2year	261	73.1
IPT	Yes	53	14.8
	No	299	83.8
CPT	Yes	76	21.3
	No	279	78.2
Comorbidities	No	307	86.0
	Yes	42	11.8
Co-medications	No	299	83.8
	Yes	57	16.0
Adherence Status	Good	302	84.6
	Poor	55	15.4

5.3 Commonly experienced ADR by study participants

At least one ADR was reported by 139 (38.9%) participants due to the use of DTG based ART regimen, and 62 (17.4%) participants reported three and more ADRs. Nearly half 172 (47.4%) of the participants had neuropsychiatric symptoms, followed by weight gain 78(21.8%) and general symptoms 37(11.4%). Skin reactions and gastrointestinal adverse drug reactions account 26(7.3%) and 11(3.1%), respectively (Table 3).

Table 3: Commonly experienced ADR characteristics of study participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022(n=357).

Characteristics	Patient developed ADR	
	Yes (N=357)	Percent %
Weight gain	78	21.8
Headache	70	19.6
Insomnia	38	10.6
Fatigue	35	9.8
Skin Rash	26	7.3
Dizziness	26	7.3
Depression	13	3.6
Anxiety	12	3.4
Nightmares	11	3.1
Nausea/vomiting	11	3.1
Fever	10	2.8
Suicidal ideation	02	0.6

5.4 Bothersome of ADRs characteristics

Figure 2 illustrates the distribution of bothersome of ADRs associated with the use of a dolutegravir-based ART regimen. The figure reveals that 45 (12.6%), 24 (6.7%), 19 (5.3%), 17 (4.8%), and 54 (15.1%) participants did not find the presence of headache, insomnia, fatigue, skin rash, and weight gain bothersome due to the dolutegravir-based ART regimen. Conversely, 25 (7.0%), 14 (3.9%), 13 (3.6%), 9 (2.5%), and 25 (7.0%) participants reported mild botheration with these symptoms, respectively. In general, a considerable segment of the ADRS, totaling 208 symptoms (58.3%), did not result in any significant botheration. On the other hand, notable portions, comprising 123 symptoms (34.5%), were reported to cause feeling of bothersome.

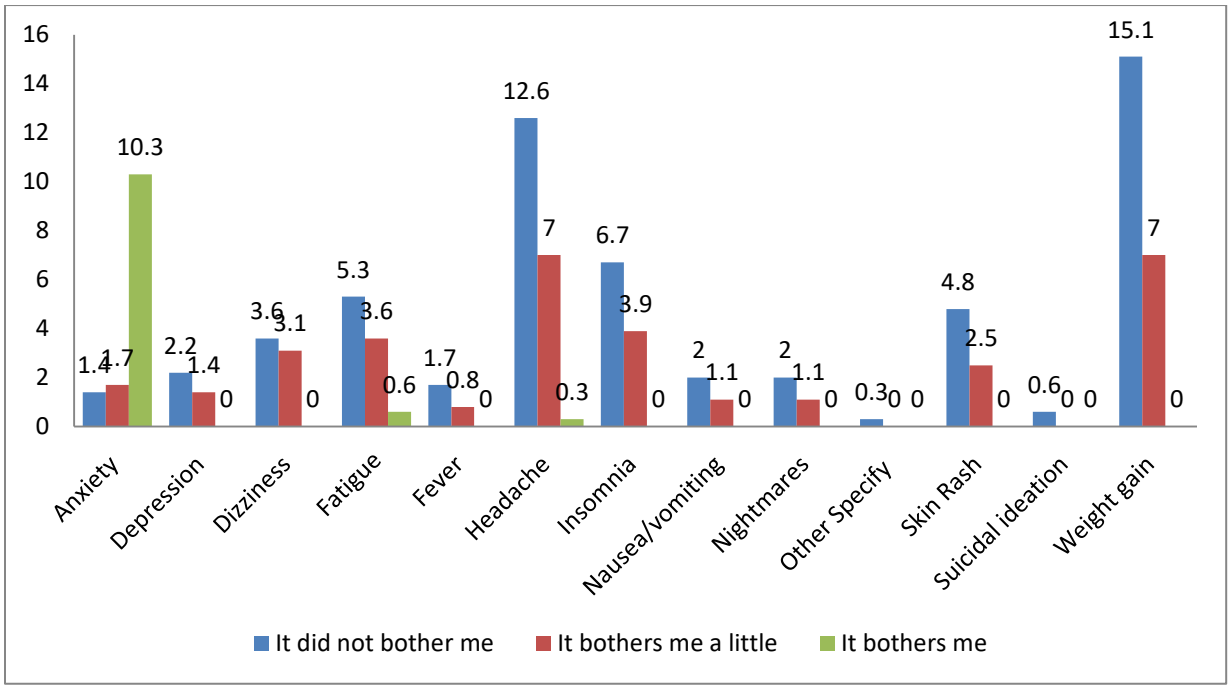

Figure 2: Bothersome of ADR characteristics of study participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022.

5.5 Predictors related with adverse reactions of study participants on dolutegravir based regimen

The results of a univariate analysis indicated that the following variables had p-values less than 0.20: marital status, residence, time since HIV diagnosis, WHO stage, CD4 count, treatment history status, duration on DTG-based cART, INH, comorbid disease, and co-medications. These variables were then included in multivariate binary logistic regressions. Three variables were significantly correlated with the incidence of ADRs, according the multivariate analysis. These statistically significant associations between ADR occurrences were found in residence, WHO Stage at entry, and co-medications. From the Adjusted Odds Ratio (AOR) for residence (AOR=0.362, 95%CI: 0.134-0.977, p=0.045), which indicate that rural residence protects the participants from ADRs as compared to participants who reside in urban. WHO stage I&II (AOR=8.582, 95%CI: 1.669-44.136, p=0.010), were 8.5 times more likely to develop ADRs than participants who were in WHO stage III&IV. Co-medications (AOR=2.606, 95%CI: 1.116-6.086, p=0.027) which indicates participants who take co-medications were more likely to experience ADRs compared to those who did not (Table 4).

Table 4: Univariate and multivariate analysis of predictors associated with adverse reactions of study participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022(n=357).

Variable	Category	Patient developed ADR		Crude OR	95% CI		P-value	Adjusted OR	95%CI		P-value
		NO N(%)	Yes N(%)		Lower bound	Upper bound			Lower bound	Upper bound	
Marital Status	Single	30(13.8)	24(17.3)	1				1			
	Married	100(45.9)	72(51.8)	0.900	0.486	1.667	0.738	1.272	0.580	2.789	0.548
	Divorced	56(25.7)	24(17.3)	0.536	0.261	1.099	0.089	0.624	0.249	1.564	0.315
	Widowed	32(14.7)	19(13.7)	0.742	0.340	1.621	0.454	0.975	0.374	2.537	0.958
Residence	Urban	191(87.6)	130(94.2)	1				1			
	Rural	27(12.4)	8(5.8)	0.435	0.192	0.988	0.047	0.362	0.134	0.977	0.045*
Duration since HIV confirmed	<5years	34(15.6)	33(23.9)	1				1			
	5-10years	82(37.6)	40(29.0)	0.503	0.273	0.925	0.027	0.603	0.230	1.581	0.304
	>=10years	102(46.8)	65(47.1)	0.657	0.371	1.162	0.149	0.908	0.353	2.340	0.842
WHO stage	1 and 2	200(91.7)	136(97.8)	4.080	1.179	14.120	0.026	8.582	1.669	44.136	0.010*
	3 and 4	18(8.3)	3(2.2)	1				1			
Current CD4 count(cells/mm3)	<200	18(9.2)	17(14.4)	1.902	0.924	3.917	0.081	1.641	0.860	3.131	0.133
	200-350	37(18.9)	31(26.3)	1.688	0.967	2.945	0.065	2.307	0.994	5.355	0.052
	>=350	141(71.9)	70(59.3)	1				1			
Treatment status	Naive	19(8.8)	25(18.1)	2.306	1.216	4.371	0.010	2.014	0.620	6.545	0.244
	Experienced	198(91.2)	113(81.9)	1				1			
Duration on DTG based ART	<2 years	64(29.8)	29(20.99)	1				1			
	>=2 years	151(70.2)	110(79.1%)	1.608	0.972	2.658	0.064	1.767	0.953	3.279	0.071
On anti TB prophylaxis	Yes	37(17.2)	16(11.7)	1				1			
	No	178(82.8)	121(88.3)	1.572	0.837	2.952	0.160	1.181	0.535	2.609	0.680
Comorbidity status	No	195(90.7)	112(83.6)	1				1			
	yes	20(9.3)	22(16.4)	1.915	1.001	3.663	0.050	2.479	0.928	6.621	0.070
Co-medication	No	193(88.5)	106(76.8)	1				1			
	Yes	25(11.5)	32(23.2)	2.331	1.312	4.139	0.004	2.606	1.116	6.086	0.027*

*Significant at p<0.05

5.6 Adherence assessment

When assessing adherence to the treatment using MMAS-8, it was observed that 88.2% of the participants had no difficulty remembering to take their medications; however, 34.5 % reported to forget bringing their medicines along while traveling. Almost all participants, 99.7 %, stated that they did not stop taking their medicine when they felt their disease was under control, and the majority, 95.2 %, reported not felt hassled about sticking to their treatment plan. The overall adherence level was 84.6 % (**Figure 3**).

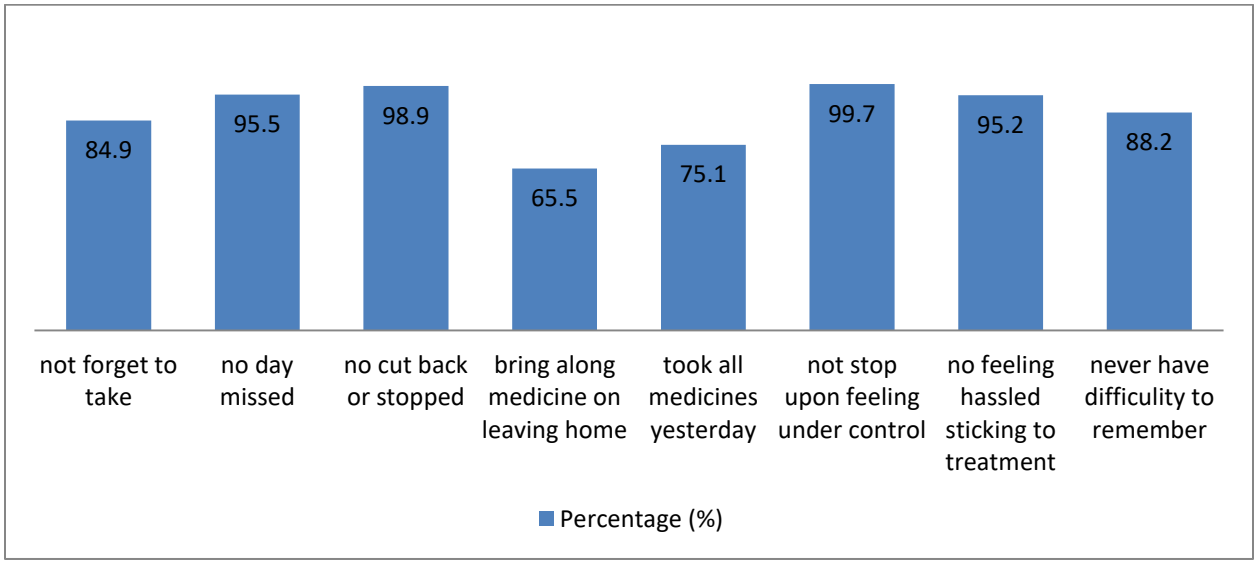

Figure 3: Individual answers to the eight items Morisky Therapeutic Adhesion Scale (MMAS-8) ofstudy participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022.

5.7 Predictors of medication adherence of study participants on dolutegravir based regimen

Gender, marital status, level of education, duration since HIV diagnosis, CD4 count, prior ART regimen, and participants in CPT were found to have p-values less than 0.20 in univariate analysis. These variables were then included in multivariate binary logistic regressions. One variable was strongly correlated with the self-reported adherence, per the multivariate analysis. According to the Adjusted Odds Ratio (AOR) for CPT (AOR=0.402, 95%CI (0.181-0.893), p=0.025) participants who were not on CPT adhered to the regimen 60% less frequently than those who were (Table 5).

Table 5: Univariate and Multivariate analysis of factors associated with poor adherence of study participants at ACSH, Mekelle city, Tigray region, Ethiopia, July to Sep, 2022(n=357).

Variable	Category	Patients' adherence level		Crude OR	95% Confidence Interval		P-value	Adjusted OR	95% CI		P-value
		adherent	Non-adherent		Lower bound	Upper bound			Lower bound	Upper bound	
Gender	Male	151(50%)	22(40%)	1				1			
	Female	151(50%)	33(60%)	1.500	0.836	2.692	0.174	1.293	0.605	2.763	0.508
Marital Status	Single	50(16.6%)	<5	1				1			
	Married	144(47.7%)	28(50.9%)	2.431	0.812	7.272	0.112	2.868	0.604	13.627	0.185
	Divorced	66(21.9%)	14(25.5%)	2.652	0.823	8.546	0.102	3.302	0.631	17.270	0.157
	Widowed	42(13.9%)	9(16.4%)	2.679	0.770	9.323	0.122	2.1502	0.447	14.006	0.297
Education	Ilitrate	58(19.3%)	18(32.7%)	1				1			
	Primary	124(41.3%)	23(41.8%)	0.598	0.299	1.193	0.144	0.606	0.265	1.385	0.235
	Secondary	52(17.3%)	7(12.7%)	0.434	0.168	1.121	0.085	0.346	0.098	1.227	0.100
	Diploma and above	66(22.0%)	7(12.7%)	0.342	0.133	0.876	0.025	0.343	0.110	1.070	0.065
Duration since HIV confirmed	<5years	59(19.6%)	8(14.5%)	1				1			
	5-10years	108(35.9%)	14(25.5%)	0.956	0.379	2.410	0.924	0.639	0.153	2.667	0.539
	>=10years	134(44.5%)	33(60.0%)	1.816	0.791	4.169	0.159	1.078	0.269	4.329	0.915
CD4count(cells/mm3)	<200	33(12.4%)	<5	0.285	0.065	1.240	0.094	0.314	0.065	1.518	0.150
	200-350	59(22.2%)	9(18.8%)	0.717	0.327	1.574	0.408	0.595	0.233	1.522	0.278
	>=350	174(65.4%)	37(77.1)	1				1			
Regimen taken before switch	ZDV based	60(23.2%)	16(32.0%)	1.561	0.806	3.022	0.187	1.736	0.776	3.881	0.179
	Non ZDV based	199(76.8%)	34(68.0%)	1				1			
On CPT	Yes	57(18.9%)	19(35.2%)	1				1			
	No	244(81.1%)	35(64.8%)	0.430	0.230	0.807	0.009	0.402	0.181	0.893	0.025*

*Significant at p<0.05

6. Discussion

DTG has been shown in several studies to be a potent and highly tolerable antiretroviral agent. Its ability to achieve rapid and sustained viral suppression has made it the drug of choice in first-line ART regimens.

A total of 357 participants were evaluated for adverse reactions and adherence to DTG- based ART. In this study, the prevalence of ADRs associated with DTG-based ART regimen was accounted for 38.9% (139/357). However, most ADRS were rated as causing no discomfort to mild discomfort. This result is consistent with others studies conducted in Northwestern Ethiopia (37.6%, 372)(Zemariam et al., 2023) and in Uganda (33%, 325) (Nabitaka et al., 2020). The ADR prevalence reported in this study was higher than in other studies conducted in Kenya (Mwanthi, 2020), Brazil (Correa et al., 2020) and in Switzerland (Elzi et al., 2017). The ADRs observed in this study may be related to the self-reported nature of the study, unlike the studies conducted by Correa *et al*. and Elzi *et al*., which were collected from patients' medical records. Furthermore, the large number of ADRs in our study may be due to the patient's subjective perception, the clinical course of HIV infection, or combination medication use.

A higher rate than our study, of at least one adverse drug reaction (43.6%, 201/461) and (81%, 76/106) was observed in patients receiving DTG based ART in South Africa (Hurbans and Naidoo, 2024) and in Brazil (Mendes et al., 2018). This difference may be due to the larger number of participants in the study compared to the Brazilian study that enrolled only 106 patients in a DTG-based ART regimen.

This study revealed that 47.4% of the reported ADRs were classified as neuropsychiatric, consistent with several other studies in which NPs-related ADRs were also commonly reported (de Boer et al., 2016, Hoffmann et al., 2017, Hongo et al., 2021). Among the neuropsychiatric ADRs, headache and insomnia were the most commonly reported, similar to studies conducted in Uganda(Namulindwa et al., 2022), Kenya (Abutika, 2020), Nigeria(Osiyemi et al., 2022) and china(Huang et al., 2017)). These findings reinforce the public health importance of neuropsychiatric disorders in PLWH treated with DTG based ART, highlighting the need for additional research to design and implement interventions.

Depression and suicidal ideation were also reported in 13 cases (3.6%) and 02 cases (0.6%), respectively. Most clinical trial studies and post market surveillance reported comparable results (Hoffmann et al., 2017, Cailhol et al., 2017). An analysis of mental disorders reported in the World Health Organization's Global Pharmacovigilance Database shows an increased risk of depression, suicide, and self- harm in patients receiving DTG. In a study conducted in Japan(Hongo et al., 2021), the incidence of adverse drug reactions related to suicidal behavior or self-harm was statistically significantly higher in patients with psychiatric disorders. These results suggest that pre-existing psychiatric disorders are a risk factor for ADRs related to suicide or self-injury in patients receiving DTG.

Weight gain and increased BMI are central issues in people living with HIV, requiring reduction of metabolic disease risk (Kolakowska et al., 2019). In this study, weight gain was 78(21.8%). This number is lower than a study conducted in South Africa in which 60.7% of the participants reported weight gain (Hurbans and Naidoo, 2024). Although weight gain after starting ART is common and beneficial to people living with HIV, significant weight gain can increase cardiovascular and metabolic complications. Therefore, additional studies are needed to confirm these findings in large multicenter cohorts (Mahale et al., 2023). Healthcare providers should inform patients receiving cART about the potential for weight gain and practical ways to avoid it, as weight gain is associated with poor health outcomes for these people.

In this study, the most commonly reported gastro-intestinal ADRs were nausea and vomiting with the rate of 3.1%(11/357), similar to study conducted in Northwestern Ethiopia (Zemariam et al., 2023). However, this rate is lower than a study conducted in Brazil(Batista et al., 2019). This discrepancy in the prevalence of gastro-intestinal ADRs may be due to differences in factors such as treatment regimens, patient populations, or study methods. Further research and consideration are needed for a comprehensive understanding of the observed differences in incidence of gastro-intestinal ADR between studies.

Dermatological reactions represent another frequent ADR among people living with HIV/AIDS on ART. In our study, we observed that skin rash was the most commonly reported dermatological ADR associated with DTG-based ART, i.e., 7.3% (26/357) similar to studies conducted in Uganda (Nabitaka et al., 2020), and Kenya (Mwanthi, 2020), but higher than the 2.29%(73/1615) reported in Brazil(Batista et al., 2019). This discrepancy might be explained for

possible variations of the study settings, regimen type and time gap in which the studies were conducted.

Many factors are associated with occurrence of ADRs among patients taking DTG based antiretroviral therapy. At multivariate analysis residence, WHO stage at entry and co-medications were found significantly associated with self-reported ADR.

In the present study, place of residence was significantly associated with adverse reactions in patients treated with dolutegravir based regimen (Adjusted OR=0.362, 95% CI 0.134-0.977). Our study found that patients in rural areas were less likely to develop adverse drug reactions to dolutegravir-based ART, in contrast to the study by Mitkie et al., which found a higher incidence of ADRs among patients from rural areas. Given that the second study was a retrospective cohort and that data were gathered by clinical chart review, there could be a reason for this variation in the research designs and study population characteristics(Mitkie et al., 2021). Further studies of these factors are needed for all-encompassing understanding of the observed differences between studies.

In this study, initiating ART at WHO clinical stage 1 or 2 was associated with a higher risk of adverse reactions (AOR=8.582, 95% CI 1.669-44.136) compared with initiating at clinical stage 3 or 4. This outcome is comparable to a study by (Abah et al., 2021), which reported that patients starting ART in WHO clinical stages 1 or 2 were 14% more likely to experience adverse responses than individuals starting in later stages. This could be explained by the fact that the study concentrated on clinical adverse responses; as a result, some clinical adverse drug reactions could be overlooked in symptomatic patients because they coincide with HIV/AIDS symptoms, leading to an underreporting of ADRs in symptomatic patients(Abah et al., 2021). In addition, the difference may be due to difference in proportion of each group of WHO clinical stage and most patients in our case were in WHO stage I and II.

This contrasts with the findings of other studies reporting that patients in WHO clinical stage III or IV are at higher risk of adverse reactions (Kindie et al., 2017, Sherfa et al., 2021). Results from a multicenter randomized controlled trial, however, indicate that starting therapy for asymptomatic HIV infection early does not seem to be linked to an increased risk of negative medication reactions (Lundgren et al., 2015). The inconsistency could potentially stem from

variations in research designs, techniques for quantifying unfavorable reactions, and kinds of cART regimens employed.

Our study shows that patients on co-medications are significantly associated with adverse reactions due to dolutegravir based first line regimens (AOR=2.606, 95%CI 1.116-6.086). Similarly a study evaluating the incidence and predictors of severe adverse drug reactions in patients receiving antiretroviral therapy in Tigray, Ethiopia reported that patients taking additional medication (adjusted hazard ratio=1.49,95% CI:1.05-2.15) are 1.5 times more likely to develop adverse drug reactions than those who do not (Gebremeskel et al., 2021). This could be due to drug interactions and concurrent toxicities between ART therapy and other medications.

Although this study found patients with comorbidity status were not significantly associated with adverse reactions in patients receiving DTG based therapy, participants with comorbidities (Crude OR=1.915,95% CI 1.001-3.663) , were nearly twice as likely to experience ADRs compared to those without comorbidities as per bivariate analysis . This is probably because very few had comorbidities in this study and might have weak immunity and were more susceptible to experience adverse reactions.

For the duration of their lives, people with HIV must take ART every day to maintain viral suppression. Patients on DTG based ART regimen at ACSH had an 84.6% self-reported drug adherence level. This aligns with findings from other studies carried out in both developed and developing nations, indicating that cART adherence level vary between 50% and 86% (Cardoso et al., 2019, Mendes et al., 2018, Ofoelo et al., 2023, Kilapilo et al., 2022, Oliveira et al., 2018). This result is less than that of the Nigeria study(Ogbonnaya et al., 2024)which revealed that (97.1%, 515) of participants had good medication adherence.

However, it is greater than those of the studies conducted in Ethiopia which reported that patients' good adherence levels were 68% and 66.3% (Tegegne et al., 2022, Koyra, 2018). The disparity in study design, and healthcare institution variations could all contribute to the discrepancies. Higher adherence to ART treatment is needed to improve clinical and immunological conditions, reduce the risk of developing ART resistance, suppress viral replication, and reduce HIV transmission.

The present study has shown the reasons for non-adherence as admitted by the study participants to be run out of pills, traveling or away from home, and felt sick or ill. Similar to this, reasons such as personal travels and too ill to take the drugs were reported in previous studies(Chijioke-Nwauche and Akani, 2021). Another study reported simple forgetting to take medications as the frequent reason for their poor adherence (Koyra, 2018, Negesa et al., 2017). A combination of strategies should be employed focusing on ways to address the common reasons associated with suboptimal adherence. A major point of importance is education and counseling the patients. Strengthening health systems by reducing drug shortages and improving training of healthcare workers will also help improve compliance.

Even though many factors were associated with poor adherence level of participants as per bivariate analysis, only patients who were not taking co-trimoxazole prophylaxis (CPT) were found to be statistically significantly as per multivariate analysis. Patients who are not taking CPT(Adjusted OR=0.402, 95% CI 0.181-0.893) were found to be 60% less likely to be adherent than those who took CPT. This can be justified by the fact that CPT usage may lead to improved health outcomes and reduced illness-related disruptions, contributing to enhanced adherence to prescribed regimens including to cART.

A study conducted by Oliveira *et al*. in the assessment of adherence to antiretroviral therapy and correlation with adverse drug effects and co-infections in people living with HIV/AIDS in the municipality of Goias State, Brazil reported that patients with low adherence (14%, 220) had higher frequency of adverse events(p=0.0009)(Oliveira et al., 2018). However, there was no difference in the reported ADRs between the adherent and non-adherent groups according to our study. Additionally, no correlation was discovered in this study with characteristics that were found in other studies to be predictors of poor adherence, such as gender, marital status, age and job status, comorbidities, and type of regimen (Inoue et al., 2023, Koyra, 2018, Tegegne et al., 2022, Namakula et al., 2023).Variations in adherence evaluation techniques, study design, and population sociodemography may be the cause.

These findings highlight the critical need to keep an eye on antiretroviral medication use in order to maintain the cART distribution strategy, particularly in light of modified new treatment regimens. It is imperative that more study be done on the side effects of antiretroviral medications in order to better understand adverse reactions linked to their usage in Ethiopia.

7. Strength and Limitations of the study

In the research area, this is the first of its kind to assess the kind of adverse medication responses and adherence linked to DTG-based ART. To reduce information bias, it collected primary data using a structured data collection format that had been pre-tested. It also searched for variables associated with ADR occurrence and adherence within the research environment. It could be the starting point for more thorough future research.

The study limitations include, its cross-sectional design, which is limited in drawing conclusions about causality. Furthermore, the results may not be representative of the national picture as they were conducted in one hospital with a relatively well-organized ART clinic.

The interviews included pre-listed questions about adverse reactions that may have omitted some important questions. Because ADRs are self-reported, no additional laboratory testing or other diagnostic procedures were performed to rule out other potential causes, which could resulted in an over reporting of ADRs.

Self-reported assessment raises the potential for social desirability bias, the patient's capacity to recall specific occurrences, difficulty in discussing adverse drug responses, and medication adherence status could have an impact on the reporting.

8. Conclusion

The rate of self-reported adverse reactions associated with DTG-based first line regimens in ACSH, Tigray region Ethiopia was common, though majority were rated as non-bothersome. Headache, insomnia and weight gain were among the most common adverse reactions being reported. Those ADRs were significantly correlated with residence, WHO stage upon admission, and co-medications.

Patients taking ART at ACSH had a suboptimal self-reported level of adherence. Lack of pill supply, traveling or being away from home, and feeling unwell were frequently cited as causes for non-adherence. According to multivariate analysis, patients who did not take CPT had an independent risk of having poor adherence to an ART regimen based on DTG.

9. Recommendations

Patients undergoing DTG-based ART should be assessed and informed about the potential adverse effects of their medications. Factors identified to be associated with ADRs should help health professionals at all levels anticipate, recognize, and minimize ADRs as soon as possible. They should also help them appreciate the necessity of close monitoring and follow-up in order to prevent the occurrence of significant ADRs.

Making medications easily accessible, offering continuous counseling services about the need of adherence, and taking early screening and illness treatment into account are all highly recommended.

Clinical documentation of ART patients by maintaining exhaustive ADR screening and monitoring should be enhanced. Additional large-scale prospective, multicenter cohort studies employing clinical and laboratory testing are required to identify treatment related adverse drug reactions.

References

ABAH, I. O., AKANBI, M., ABAH, M. E., FINANGWAI, A. I., DADY, C. W., FALANG, K. D., EBONYI, A. O., OKOPI, J. A., AGBAJI, O. O. & SAGAY, A. S. 2015. Incidence and predictors of adverse drug events in an African cohort of HIV-infected adults treated with efavirenz. *Germs,* 5**,** 83.

ABAH, I. O., DAYOM, W. D., DANGIWA, D. A., ADEREMI-WILLIAMS, R., ANEJO-OKOPI, J., AGBAJI, O. O., KANKI, P. & AGUIYI, J. C. 2021. Comparative incidence of adverse drug reaction during the first and subsequent year of antiretroviral therapy in a Nigerian HIV infected Cohort. *African Health Sciences,* 21**,** 1027-1039.

ABAH, I. O., NCUBE, N., BRADLEY, H. A., AGBAJI, O. O. & KANKI, P. 2018. Antiretroviral Therapy-associated adverse drug reactions and their effects on virologic Failure-a retrospective cohort study in Nigeria. *Current HIV Research,* 16**,** 436-446.

ABUTIKA, R. A. 2020. *Burden of Neuropsychiatric Adverse Effects and Changes in Weight Among Hiv Infected Patients Switched From an Efavirenz Based to a Dolutegravir Based First Line Regimen at the Kenyatta National Hospital.* University of Nairobi.

ANBESSA, O., HAWULTE, B., DINGETA, T. & BIRHANU, A. 2024. Incidence and Predictors of Severe Adverse Drug Reactions among Patients on Antiretroviral Drugs in Harari Regional State, Eastern Ethiopia. *The Canadian Journal of Infectious Diseases & Medical Microbiology= Journal Canadien des Maladies Infectieuses et de la Microbiologie Médicale,* 2024.

ANSTETT, K., BRENNER, B., MESPLEDE, T. & WAINBERG, M. A. 2017. HIV drug resistance against strand transfer integrase inhibitors. *Retrovirology,* 14**,** 1-16.

AYELE, T. A., WORKU, A., KEBEDE, Y., ALEMU, K., KASIM, A. & SHKEDY, Z. 2017. Choice of initial antiretroviral drugs and treatment outcomes among HIV-infected patients in sub-Saharan Africa: systematic review and meta-analysis of observational studies. *Systematic reviews,* 6**,** 1-14.

BATISTA, C. J. B., CORREA, R. G., EVANGELISTA, L. R., FLECK, K., SILVA, L., RENAUD, F., VITORIA, M., DOHERTY, M. & BENZAKEN, A. S. 2019. The Brazilian experience of implementing the active pharmacovigilance of dolutegravir. *Medicine,* 98.

BENSON, C., WANG, X., DUNN, K., LI, N., MESANA, L., LAI, J., WONG, E., CHOW, W., HARDY, H. & SONG, J. 2020. Antiretroviral adherence, drug resistance, and the impact of social determinants of health in HIV-1 patients in the US. *AIDS and Behavior,* 24**,** 3562-3573.

CAILHOL, J., ROUYER, C., ALLOUI, C. & JEANTILS, V. 2017. Dolutegravir and neuropsychiatric adverse events: a continuing debate. *Aids,* 31**,** 2023-2024.

CARDOSO, T. S., COSTA, J. D. O., REIS, E. A., SILVEIRA, M. R., BONOLO, P. D. F., SANTOS, S. F. D. & CECCATO, M. D. G. B. 2019. Which antiretroviral regimen is associated with higher adherence in Brazil? A comparison of single, multi, and dolutegravir-based regimens. *Cadernos de saude publica,* 35**,** e00115518.

CATALANO, A. 2022. Adherence Required On Dolutegravir.

CEVIK, M., ORKIN, C. & SAX, P. E. Emergent resistance to dolutegravir among INSTI-naive patients on first-line or second-line antiretroviral therapy: a review of published cases. Open Forum Infectious Diseases, 2020. Oxford University Press US, ofaa202.

CHIJIOKE-NWAUCHE, I. & AKANI, Y. 2021. Influencing factors of adherence to antiretroviral drugs among people living with HIV in South-South Nigeria. *Saudi J Med Pharm Sci,* 7**,** 145-52.

CHILAMBE, M., KALUNGIA, A. C., MANGANI, A. & MUNKOMBWE, Z. 2019. An analysis of pharmacovigilance case reports of adverse drug events attributable to dolutegravirbased antiretroviral treatment for HIV in Zambia. *Medical Journal of Zambia,* 46**,** 305-313.

CORREA, A., MONTEIRO, P., CALIXTO, F., BATISTA, J. D. A. L., DE ALENCAR XIMENES, R. A. & MONTARROYOS, U. R. 2020. Dolutegravir: Virologic response and tolerability of initial antiretroviral regimens for adults living with HIV. *PLoS One,* 15**,** e0238052.

DAHIYA, S. 2018. A systematic review of risk factors of adverse drug reactions in hospitalized patients. *Asian J Pharm Clin Res,* 11**,** 25-29.

DE BOER, M. G., VAN DEN BERK, G. E., VAN HOLTEN, N., ORYSZCYN, J. E., DORAMA, W., AIT MOHA, D. & BRINKMAN, K. 2016. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *Aids,* 30**,** 2831-2834.

DO, H. M. 2011. *Antiretroviral therapy (ART) adherence among People Living with HIV/AIDS (PLHIV) in the North of Vietnam: a Multi-method Approach.* Queensland University of Technology.

EJIGU, A., GEHZU, M. & HAILESELASSIE, W. 2018. Adverse drug reactions causing treatment change among patients taking highly active antiretroviral therapy in health care facilities of Mekelle, Ethiopia. *Journal of Applied Pharmaceutical Science,* 8**,** 104-110.

ELZI, L., ERB, S., FURRER, H., CAVASSINI, M., CALMY, A., VERNAZZA, P., GÜNTHARD, H., BERNASCONI, E., BATTEGAY, M. & GROUP, S. H. C. S. 2017. Adverse events of raltegravir and dolutegravir. *Aids,* 31**,** 1853-1858.

FEDERAL MINISTRY OF HEALTH ETHIOPIA, F. 2018. National consolidated guidelines for comprehensive HIV prevention, care and treatment. Federal Ministry of Health Addis Ababa, Ethiopia.

FMHACA, F., MEDICINE AND HEALTH CARE ADMINISTRATION AND CONTROL AUTHORITHY OF ETHIOPIA 2016. Importance of Active surveillance and Cohort Event monitoring on ARV medicines in Ethiopia. *Pharmacovigilance center in Ethiopia,* volume 6.

GEBREMESKEL, T. G., GEBREYOWHANS, D., ABRHA GESESEW, H. & WARD, P. R. 2021. Incidence and Predictors of Severe Adverse Drug Reaction Among Patients on Antiretroviral Therapy in Tigray, Ethiopia: A Retrospective Cohort Study. *HIV AIDS (Auckl),* 13**,** 641-649.

HAILU, A. D. & MOHAMMED, S. A. 2020. Adverse drug reaction reporting in Ethiopia: systematic review. *BioMed research international,* 2020**,** 1-12.

HOFFMANN, C., WELZ, T., SABRANSKI, M., KOLB, M., WOLF, E., STELLBRINK, H. J. & WYEN, C. 2017. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV medicine,* 18**,** 56-63.

HONGO, H., NAGAO, T., NAKAMURA, K., KITAICHI, T., MAENO, Y., TOKUNAGA, T., FUKUDA, A. & KOGA, I. 2021. Safety and effectiveness analysis of dolutegravir in patients with HIV-1: interim report of post-marketing surveillance in Japan. *Advances in Therapy,* 38**,** 4480-4504.

HUANG, X., LI, H., MEYERS, K., XIA, W., MENG, Z., LI, C., BAI, J., HE, S., CAI, W. & HUANG, C. 2017. Burden of sleep disturbances and associated risk factors: a cross-

sectional survey among HIV-infected persons on antiretroviral therapy across China. *Scientific reports,* 7**,** 3657.

HURBANS, N. & NAIDOO, P. 2024. Efficacy, safety, and tolerability of dolutegravir-based ART regimen in Durban, South Africa: a cohort study. *BMC Infectious Diseases,* 24**,** 343.

INOUE, Y., OKA, S., YOKOYAMA, S., HASEGAWA, K., MAHLICH, J., SCHAEDE, U., HABUKA, N. & MURATA, Y. Medication Adherence of People Living with HIV in Japan—A Cross-Sectional Study. Healthcare, 2023. MDPI, 451.

KILAPILO, M. S., SANGEDA, R. Z., BWIRE, G. M., SAMBAYI, G. L., MOSHA, I. H. & KILLEWO, J. 2022. Adherence to Antiretroviral Therapy and Associated Factors Among People Living With HIV Following the Introduction of Dolutegravir Based Regimens in Dar es Salaam, Tanzania. *J Int Assoc Provid AIDS Care,* 21**,** 23259582221084543.

KINDIE, E., ALAMREW ANTENEH, Z. & WORKU, E. 2017. Time to development of adverse drug reactions and associated factors among adult HIV positive patients on antiretroviral treatment in Bahir Dar City, Northwest Ethiopia. *PloS one,* 12**,** e0189322.

KOLAKOWSKA, A., MARESCA, A. F., COLLINS, I. J. & CAILHOL, J. 2019. Update on adverse effects of HIV integrase inhibitors. *Current treatment options in infectious diseases,* 11**,** 372-387.

KOYRA, H. 2018. Adherence to antiretroviral therapy among adult persons living with HIV/AIDS in Southern Ethiopia. *Int J Virol AIDS,* 5**,** 10.23937.

KUMARASAMY, N., PRABHU, S., CHANDRASEKARAN, E., POONGULALI, S., PRADEEP, A., CHITRA, D., BALAKRISHNAN, R. & BENSON, C. A. 2019. Safety, tolerability, and efficacy of generic dolutegravir-containing antiretroviral therapy regimens among South Indian human immunodeficiency virus-infected patients. *Clinical Infectious Diseases,* 68**,** 1048-1051.

LI, G., JING, X., ZHANG, P. & DE CLERCQ, E. 2021. Antiviral classification. *Encyclopedia of Virology***,** 121.

LUNDGREN, J. D., BABIKER, A. G., GORDIN, F., EMERY, S., GRUND, B., SHARMA, S., AVIHINGSANON, A., COOPER, D. A., FÄTKENHEUER, G. & LLIBRE, J. M. 2015. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *The New England journal of medicine,* 373**,** 795-807.

MAHALE, P. R., PATEL, B. S., KASMANI, N. & PATEL, B. 2023. Treatment outcomes of dolutegravir-versus efavirenz-based highly active antiretroviral therapy regimens among treatment-naive people living with HIV. *Cureus,* 15.

MENDES, J. C., BONOLO, P. D. F., CECCATO, M. D. G. B., COSTA, J. D. O., REIS, A. M. M., DOS SANTOS, H. & SILVEIRA, M. R. 2018. Adverse reactions associated with first-line regimens in patient initiating antiretroviral therapy. *European journal of clinical pharmacology,* 74**,** 1077-1088.

MINISTRY OF HEALTH, A. A. E. 2023. National HIV prevention road map 2023-2027.

MITKIE, A. A., BEKELE, F. B. & DEBISO, A. T. 2021. Predictors of adverse drug reaction among adult HIV-infected patients on antiretroviral therapy in government hospitals of Kaffa Zone, Ethiopia; November 2018: a retrospective cohort. *Pan African Medical Journal,* 38.

MONDI, A., COZZI-LEPRI, A., TAVELLI, A., RUSCONI, S., VICHI, F., CECCHERINI-SILBERSTEIN, F., CALCAGNO, A., DE LUCA, A., MAGGIOLO, F. & MARCHETTI, G. 2019. Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort. *Journal of the International AIDS Society,* 22**,** e25227.

MORISKY, D. E. 2008. Predictive validity of a medication adherence measure for hypertension control. *Journal of clinical hypertension,* 10**,** 348-354.

MWANTHI, C. K. 2020. *Safety, Tolerability and Adherence of Dtg-based Regimen Among Adult Hiv Patients Attending Kenyatta National Hospital.* University of Nairobi.

NABITAKA, V. M., NAWAGGI, P., CAMPBELL, J., CONROY, J., HARWELL, J., MAGAMBO, K., MIDDLECOTE, C., CALDWELL, B., KATUREEBE, C. & NAMUWENGE, N. 2020. High acceptability and viral suppression of patients on Dolutegravir-based first-line regimens in pilot sites in Uganda: a mixed-methods prospective cohort study. *PloS one,* 15**,** e0232419.

NAMAKULA, E., MUGERWA, H., KITUTU, F., KAWUMA, A. N., KIGUBA, R. & KALYANGO, J. N. 2023. Prevalence and factors associated with suboptimal adherence to dolutegravir-based regimens among people living with HIV in a specialized clinic in Kampala, Uganda.

NAMULINDWA, A., WASSWA, J. H., MUYINDIKE, W., TAMUKONG, R. & OLORO, J. 2022. Prevalence and factors associated with adverse drug events among patients on dolutegravir-based regimen at the Immune Suppression Syndrome Clinic of Mbarara Regional Referral Hospital, Uganda: a mixed design study. *AIDS Research and Therapy*, 19**,** 1-8.

NASREDDINE, R., FLORENCE, E., VANDERCAM, B., MOUTSCHEN, M., GOFFARD, J.-C., DE MUNTER, P., DELFORGE, M., MARINUS, W. & DE WIT, S. 2020. Effectiveness of dolutegravir-based antiretroviral therapy in a real-world setting in a Belgian cohort of 4101 HIV patients. *Aids,* 34**,** 1151-1159.

NEGESA, L., DEMEKE, E. & MEKONNIN, W. 2017. Adherence to antiretroviral therapy and factors affecting among people living with HIV/AIDS and taking antiretroviral therapy, Dire Dawa Town, Eastern Ethiopia. *J Infect Dis Treat,* 3**,** 5.

OFOELO, E. C., INNOCENT, D. C., OFOELO, I. L., VASAVADA, A. & ENEH, S. C. 2023. Prevalence of adverse drug effects of anti-retroviral drugs on hiv-positive patients receiving anti-retroviral treatment in General Hospital Onitsha, Anambra, Nigeria. *Academic Journal of Health Sciences: Medicina Balear,* 38**,** 136-144.

OGBONNAYA, L. U., ONAH, C. K., AZUOGU, B. N., AKPA, C. O., OKEKE, K. C., NWACHUKWU, V. N., STEPHEN-EMEYA, A., ASAGA, I. U. & UMEOKONKWO, C. D. 2024. Adverse drug reactions, adherence, and virologic outcomes in adult patients on dolutegravir-based antiretroviral therapy at a tertiary hospital, southeast Nigeria. *Ghana Medical Journal,* 58**,** 101-108.

OLIVEIRA, L. D. S., CAIXETA, L. M., MARTINS, J. L. R., SEGATI, K. D., MOURA, R. S., DAHER, M. C. & PINTO, E. M. H. 2018. Adherence to antiretroviral therapy and correlation with adverse effects and coinfections in people living with HIV/AIDS in the municipality of Goiás State. *Revista da Sociedade Brasileira de Medicina Tropical,* 51**,** 436-444.

OSIYEMI, A. O., OWOAJE, E., MUNDT, J. M., OLADEJI, B., AWOLUDE, O., OGUNNIYI, A., OKONKWO, P., BERZINS, B. & TAIWO, B. O. 2022. Sleep disturbance and associated factors among Nigerian adults living with HIV in the dolutegravir era. *Frontiers in Sleep,* 1**,** 963529.

SHERFA, A., HAILE, D., YIHUNE, M. & SAKO, S. 2021. Incidence and predictors of Adverse Drug Reaction (ADR) among adult HIV positive patients on anti-retroviral treatment in Arba Minch town public health facilities, southern Ethiopia: A retrospective cohort study, 2020. *Plos one,* 16**,** e0251763.

SHUBBER, Z., MILLS, E. J., NACHEGA, J. B., VREEMAN, R., FREITAS, M., BOCK, P., NSANZIMANA, S., PENAZZATO, M., APPOLO, T. & DOHERTY, M. 2016. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. *PLoS medicine,* 13**,** e1002183.

SOARES, Y. K. D. C. & ARAÚJO, T. M. E. D. 2020. Evidences on the effectiveness of text messages in the adherence to antiretroviral therapy in adults. *Revista Gaúcha de Enfermagem,* 41**,** e20190242.

TEGEGNE, D., MAMO, G., NEGASH, B., HABTE, S., GOBENA, T. & LETTA, S. 2022. Poor adherence to highly active antiretroviral therapy and associated factors among people living with HIV in Eastern Ethiopia. *SAGE Open Medicine,* 10**,** 20503121221104429.

TEKLE, A., TSEGAYE, A. & KETEMA, T. 2024. Adherence to Anti-Retroviral Therapy (ART) and Its Determinants Among People Living with HIV/AIDS at Bonga, Kaffa, South-West Ethiopia. *Patient preference and adherence***,** 543-554.

UNAIDS, U. N. P. O. H. A. 2023. AIDS statistics–2022 fact sheet. *Accessed April,* 26.

WADESANGO, L. 2022. *Dolutegravir reported adverse drug reactions: a systematic review.* Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

WELDEGEBREAL, F., MITIKU, H. & TEKLEMARIAM, Z. 2016. Magnitude of adverse drug reaction and associated factors among HIV-infected adults on antiretroviral therapy in Hiwot Fana specialized university hospital, eastern Ethiopia. *Pan African Medical Journal,* 24.

WHO, W. H. O. 2018. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization.

WHO, W. H. O. 2022. *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations,* World Health Organization.

YADAV, G., KUMAR, P., KUMAR, Y. & SINGH, P. K. 2018. Dolutegravir, second generation integrase inhibitor: A new hope for HIV patient. *European Journal of Molecular and Clinical Medicine,* 5**,** 20-29.

YUNITA, E. P., WARDANI, R. N. K. & SIDHARTA, B. 2023. Correlation between knowledge level, side effect severity, family support, and antiretroviral therapy adherence in HIV/AIDS patients in Greater Malang, East Java, Indonesia. *Pharmacia,* 70**,** 1213-1222.

ZEMARIAM, A. B., TADESSE, Y. B. & KASSAW, A. T. 2023. Prevalence and Patterns of Adverse Drug Events Among Adult Patients with Human Immune Virus Infection on Dolutegravir-Based Antiretroviral Drug Regimens in Amhara Comprehensive Specialized Hospitals, Northwest Ethiopia: A Multicenter Retrospective Follow-Up Study. *HIV/AIDS (Auckland, NZ),* 15**,** 271.

ZUCKER, I. & PRENDERGAST, B. J. 2020. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biology of sex differences,* 11**,** 1-14.

Annexes

Annex 1: Participant information and consent form

Hello, My name is_____. I am collecting data for a research on the assessment of prevalence of self-reported adverse reactions and adherence of Dolutegravir (DTG) containing antiretroviral therapy regimens among patients in Ayder Comprehensive Specialized Hospital., Mekelle city, Tigray region, Ethiopia. This study is being conducted by Goitom Belay, a Master of Science Degree in Pharmacy Practice graduating student at Addis Ababa university. The aim of this study is to assess prevalence self-reported adverse reactions and adherence of Dolutegravir (DTG) containing antiretroviral therapy regimens among patients in Ayder Comprehensive Specialized Hospital, Mekelle city, Tigray region, Ethiopia.

Your willingness and participation in this study is important to provide information regarding self-reported adverse reactions and adherence of Dolutegravir based first line therapy. It will identify gaps in patients and health care system, pass the information to responsible bodies to manage adverse effects and improve adherence to HIV/AIDS patients who initiated or switched to Dolutegravir based first line therapy.

Participation is based on your full willingness. Your name will not be mentioned in this questionnaire and the information you give will be kept confidentially and only used for research purpose. If you found a question not comfortable, you can skip. Your right not to participate is respected at any time. There will be no consequences to you if you decide not to participate, and this will not affect your treatment.

If you have any concern regarding this study you can communicate me through the following address.

Phone number: +251-914383964 Email: Begoitom12@gmail.com

Are you willing to continue Yes ☐ No ☐

Annex 2: Data Collection Form

Part I- Socio-demographic		
	Age	_____Years
	Sex	1. Male 2. Female
	Weight(Kg); Height(M)	_____Kg;_____Meter
	Body Mass Index(Kg/m2)	_____Kg/m2
	Marital status	1. Single 2. Married 3. Divorced 4. Widowed 5. Separated
	Educational status	1. Illiterate 2. Grade 1-8 3. Grade 9-10 4. Diploma and above
	Residence	1. Urban 2. Rural
	Religion	1. Orthodox 2. Islam 3. Catholic 4. Protestant 5. Other, specify
	Occupational status	1.Employeed 2. Not employed
Part II- Clinical and laboratory data		
	Date confirmed HIV+	____/____/____E.C
	WHO Stage	1. I 2. II 3. III 4. IV
	Current CD4 count	
	Treatment Naive	1. Yes 2. No 3. Not reported
	Drug of initial regimen at initiation of ART	1. ZDV/3TC/NVP 2. ZDV/3TC/EFV 3.TDF/3TC/NVP 4.TDF/3TC/EFV 5. Other __
	Starting date of initial regimen	_____years
	Current Regimen patients on	TDF/3TC/DTG (TLD) 2. ABC/3TC/DTG 3. Others
	Starting date of current regimen	_____years
	Number of pills taken per day and frequencies	One pill; a day 2. One pill: twice a day(1 pill morning:1 pill evening)
	On anti TB prophylaxis	Yes 2. No
	On Bactrim (Cotri)	Yes 2. No
	Comorbidities status	Hypertension 2. Heart failure 3. Diabetes 4. Hepatitis 5. TB 6. None 7. Others_____
	Number of non HIV/AIDS medications	1-2 2. 3-4 3. 4-5 4. >5 5. None

Part III: Adverse drug reactions

Following initiation or switch to DTG, have you experienced the following symptoms with in four weeks?		I did not have any of the symptoms	I had the specified symptom and_____			
			It did not bother me	It bothered me a little	It bothered me	It bothered me a lot
1	Headache					
2	Dizziness					
3	Fatigue					
4	Insomnia					
5	Nightmares					
6	Depression					
7	Anxiety					
8	Nausea or vomiting					
9	Weight gain					
10	Skin Rash					
11	Fever					
12	Suicidal ideation					
	Other Specify					

Part IV:Morisky 8-Item Medication Adherence Questionnaire

	Yes	No
Do you sometimes forget to take your medicine?		
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine? If yes why?		
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
When you travel or leave home, do you bring along your medicine?		
Did you take all your medicines yesterday? If not why?		
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
How often do you have difficulty remembering to take all your medicine? A. Never/rarely B. Once in a while C. Sometimes D. Usually E. All the time		

Annex 3: Participant information and consent form in Tigrigna language

ናይ ፍቓደኝነት መሕተቲ ቅጥዒ

ሰላም!

ሽመይ_____ይበሃል። ኣነ ናብዚ ዝመፃእኩሉ ምኽንያት ብዛዕባ አብ ዓይደር ዝርከቡ ዲትጂ ዝበሃል መድሃኒት ጸረ ኤች አይ ቪ ኤድስ ዝወስዱ ዘሳዓበሎም ጎናዊሳዕቤን ንጉቡእ አጠቃቅማን ዝምልከት ዓሊሙ ዝተዳለወ መፅናዕቲ ቃለመሕተት ንምክያድ እዩ። እዚ መፅናዕቲ ብተምሃራይ ጎይትኦም በላይ ኣብ አዲስአበባ ዩኒቨርስቲ ናይ ማስተርስ ድግሪ ተመራቂ ዝኾነ ዝካየድ እዩ። ናይ ዚመፅናዕቲ ዕላማ ድማ ኣብ ዓይደር ዝርከቡ ዲትጂ ዝበሃል መድሃኒት ጸረ ኤች አይ ቪ ኤድስ ዝወስዱ ዘስዓበሎም ጎናዊ ሳዕቤን ንጉቡእ አጠቃቅማ ንዝምልከት ንምድህሳስን ዘለዉ ፀገማት ንምፍላጥን ናይ መፍትሒ ሓሳብ ንምርካብን እዩ። አብዚ ከባቢ 15 ደቂቓ ግዚኦም/ኤን ብምጥቃም ንኽሳተፉ/ፋብትሕትና ይሓትት። ናቶም/ተን ተበግሶን ድልዉነትን ድማ ነዚ መፅናዕቲ አብ ዓይደር ዝርከቡ ዲትጂ ዝበሃል መድሓኒት ረጂመን ጸረ ኤች አይ ቪ ኤድስ ዝወስዱ ዘስዓበሎም ጎናዊ ሳዕበን ንጉቡእ አጠቃቅማንንምግምጋም ኣዝዩ ሓጋዛይ እዩ። ኣብዚ መፅናዕቲ ንምስታፍ ሙሉእ ብሙሉእ ኣብዓርሰ ፍቓድ ዝተመስረተ እዩ።ብዛዕባ ዉልቀ መንነቶም/ተን ዝሕብር ምንም ነገር ኣይህሉን።ምስጢርነቱ ኣዝዩ ሕልዉ እዩ።እቲ ሕቶ እንተዘይጥዕምዎም/ወን ንገሊኡ ወይከዓ ንኩሉ ናይዘይምምላስ መሰሎም/ለን ሕልው እዩ። ብዛዕባ እቲ መፅናቲ ሕቶታት እንተሃልይዎም/ወን በዚ ዝስዕብ ኣድራሻ ይሕተቱ/ታ።

ጎይትኦም በላይ ስ/ቁ 0914383964 Email- begoitom12@gmail.com

ኣብዚ መፅናዕቲ ንምስታፍ ፍቓደኛ ድዮም/የን?

ሀ/እወ ለ/ፍቓደኛ ኣይኮንኩን

Annex 4: Data Collection Form in Tigrigna language

ሓቤሪታ መሰብሰቢ ቅጥዒ

ተ.ቁ	ሓቤረታ	ምድብ
ክፋል I- ማሕበረኢኮኖሚያዊኩነታትን		
	ካርድቁጽሪ	_____
	ዕድመ	_____ዓመት
	ጾታ	1. ተባዕታይ 2. አንስታይ
	ክብደት :ቁመት	_____ኪሎግራም: ሜትር_____
	ቦዲማስኢንዴክስ(BMI)	_____ኪሎግራም፡ሜትርስኬር
	ኩነታትሓዳር	1. ዘይተመርዐወ/ት 2. ዝተመርዐወ/ት 3. ዝፈትሐ/ት 4. ሰብኣያ/ሰበይቱዝሞታ/ተት 5. ዝትፈላለዩ
	ደረጃትምህርቲ	1. ስሩዕትምህርቲዘይተምሃረ／ት 2. ቀዳማይብርኪ(1-8) 3. ካልአይብርኪ (9-10) 4. ዲፕሎማንልዕሊኡን
	መንበሪ	1.ከተማ 2. ገጠር
	ሃይማኖት	1. ኦርቶዶክስ 2.ሙስሊም 3. ካቶሊክ 4. ፕሮቴስታንት 5. ካሊእ, ይገለጽ
	ናይስራሕኩነታት	1 ናይ ስራሕ ቁፃር እየ 2. ምንም ዓይነት ናይ ስራሕቁፃር ኣይብለይን

ክፋል II: ምስ ሕማምን መድሓኒትን ዝተትሓሓዙ ሓበሬታታት		
	ኤች አይ ቪ ፖዝቲቭ ምካኖም ዝፈለጥሉ ዕለት	_____ዓ.ም
	ብርኪ ሕክምናዊ ምርመራ ትካል ዓለምለኻዊ ሕክምና(WHO stage)	1. I 2. II 3. III 4. IV
	ናይ ቀረባ ግዜ ስዲ 4 አቆጻጽራ (CD4 count)	
	እቲ መድሓኒት ናይ መጀመርታኦም ድዩ?	1. እወ 2. አይኮነን 3. አይፍለጥን
	ናይ መጀመርቶም ተዘይኮይኑ፣እንታይ ዓይነት መድሓኒት ይጥቀሙ ነይሮም?	1. ZDV/3TC/NVP 2. ZDV/3TC/EFV 5.TDF/3TC/NVP 6.TDF/3TC/EFV 7. ካሌእእንተኮይኑይግለጹ_____
	ናይ መጀመርታ መድሓኒቶም ዝጀመርሉ ግዜ	_____ዓ.ም
	ሕጂ ዝወስድዎ ጸረ ኤች አይ ቪ መድሃኒት ረጂመን እንታይ እዩ?	1 TDF/3TC/DTG (TLD) 2 ABC/3TC/DTG 3. Other
	እቲ ሕጂ ዝወስድዎ መድሓኒት ዝጀመርሉ ግዜ	_____ዓ.ም
	ክንደይ ዝአክል ፍረ መድሓኒት ይወስዱ? አብ መዐልቲከ ክንደግዘ ይወስዱ?	1 ፍረ፤አብመዓልቲ 1 ፍረ፤አብ መዓልቲ ክልተ ግዘ(1ፍረንጉሆ፤ 1ፍረምሸት)
	ናይ ቲቢ ሕማም መከላኸሊ መድሓኒት ይወስዱ ዶ?	1. አወ 2. አይፋሉን
	ባክትሪም (Cotri) መድሓኒት ይወስዱ ዶ?	1. እወ 2. አይፋሉን
	ኩነታት ጎናዊ ሕማማት	1.በዝሒ 2. ናይ ልቢ ሕማም 3. ሕማም ሸኮር 4. ሂፍሸዋ (ሕማም ጸላም ከብዲ) 4. ቲቢ 5. ካሊእ እንተልዩይግለጹ
	በዝሒካብናይኤችአይቪመድሓኒትወጻኢዝወስድዎመድሓኒት	1. 1-2 2. 3-4 3. 4-5 4. >5

ክፋል III፡ ምስ መድሓኒት ዝተታሓሓዘ ኣብ ሰዉነት ዝረኣዩ ዘይተለመዱ ምልክታት ዝምልከት						
	መድሓኒት ዲቲጂ ዝበሃል ጸረ ኤች ኣይ ቪ ምስ ተጀመረሎም ወይም ምስተቐየረሎም ሲዒቡ ኣብውሽጢ ኣርባዕተ ሰሙን፣ እዞም ዝስዕቡ ምልክታት ነይሮምዎም ዶ?	ኣቲ ዝተገለጸ ምልከት ኣይነበረንን	እቲ ዝተገልጸ ምልክት ነይሩኒ እዩ መጠን ጉድኣቱ ድማ.... ነይሩ			
			ጸገም ኣይፈጥረለይን ነይሩ	ንእሽተይ ጸገም ይፈጥረለይ ነይሩ	ሓያል ጸገም ይፈጥረለይ ነይሩ	ኣዝዩ ሓያል ጸገም ይፈጥረለይ ነይሩ
	ርእሲ ሕማም					
	ስምዒት ርእሲ ምዛር(ምንጽርራው)					
	ድካም ወይም ጉልበት ምስኣን					
	ምድቃስ ምጅማር ወይም ደቂስካ ምጽናሕ ምጽጋም					
	ለይቲ ለይቲ ምብህራር					
	ስማዒት ሓዘን፣ድብርቲ					
	ስምዒት ጭንቀት					
	ተውሳክ ወይም ምምላስ					
	ኣብ ኣካላት ለውጢ ምርኣይ ንኣብነት ክብደት ምዉሳኽ					
	ናይ ቆርበት ጸገም ከምሽፍታ፣ድርቀት ወይም ምሕካኽ					
	ረስኒ/ምቆት፣ምንቅጥቃጥ ወይ ምርሃጽ					
	ዓርስኻ ናይ ምጥፋእ ሓሳብ					
	ካሌእ እንተሊዩ ይግለጹ/ጻ_____					

ክፋል IV፡ናይ ተሓከምቲ ናይ መድሓኒት ኣዎሳስዳ ዝምልክት		
1	ሓደ ሓደ ጊዜ መድሓኒት ምውሳድ ረሲዖም ይፈልጡ ዶ ?	1. እዎ 2. ኣይፋሉን
2	ሓደ ሓደ ጊዜ ሰባት ካብ ምርሳዕ ወጻኢ መድሓኒት ከይወሰዱ ይተርፉ እዮም። ኣብ ዝሓለፈ ክልተ ሰሙን መድሓኒት ከይወሰዱ ዘሕለፍዎ መዓልቲ ነይሮም ዶ?	1. እዎ 2. ኣይፋሉን
	መልሶም እዎ እተኮይኑ ንምታይ ?	
3	ሕማሞም ስለዝተባኣሰ ሓኪሞም ከየማኸሩ መድሓኒቶም ኣቓሪጾም ዶ ይፈልጡ ?	1. እዎ 2. ኣይፋሉን
4	ኣብ መንገሻ ጊዜ መድሓኒቶም ብትክክል ዶ ይዎስዱ ?	1. እዎ 2. ኣይፋሉን
5	ትማሊ ኩሉ መድሓኒቶም ዎሲዶም ዶ ?	1. እዎ 2. ኣይፋሉን
	መልሶም ኣይፋሉን እተኮይኑ ንምንታይ ?	
6	ሕማመይ ቀኒሱ/ ሕሹኒ ኢሎም መደሓኒቶም ጠጠው ኣቢሎም ዶ ይፈልጡ ?	1. እዎ 2. ኣይፋሉን
7	መድሓኒት ዘይምዉሳድ ናይ ሓደ ሓደ ሰባት ፀገም እዩ። መድሓኒቶም ብትእዛዝ መሰረት ንምዉሳድ ይሰላቸ ዶ ?	1. እዎ 2. ኣይፋሉን
8	ኩሉ መድሓኒቶም ንምዉሳድ ዝኸበደኩም ክንደይ ጊዜ እዩ ?	1. ፈፂሙ 2. ብዝኾነ ጊዜ ሓደ ጊዜ 3. ሓደ ሓደ ጊዜ 4. ብተደጋጋሚ ግዜ 5. ኩሉ ግዘ